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DEFENSE HEALTH CARE

Research on Hyperbaric Oxygen Therapy to Treat Traumatic Brain Injury and Post-Traumatic Stress Disorder

GAO-16-154

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GAO Highlights

Highlights of GAO-16-154, a report to congressional committees

Why GAO Did This Study

TBI and PTSD are signature wounds for servicemembers returning from the conflicts in Iraq and Afghanistan. Within the military, the majority of TBI cases have been classified as mild. Studies have found that one-third or more of servicemembers with mild TBI also have PTSD. As an alternative to traditional treatments, some researchers have studied the use of HBO_2 therapy, which delivers higher levels of oxygen to the body inside of pressurized hyperbaric chambers to promote healing. The Joint Explanatory Statement accompanying the Consolidated and Further Continuing Appropriations Act, 2015, included a provision for GAO to review the use of HBO_2 therapy to treat TBI and PTSD.

This report identifies and describes published research on the use of HBO_2 therapy for these conditions. GAO conducted a literature review for relevant articles published in peer-reviewed journals during the most recent 10-year period, from January 1, 2005 through April 6, 2015. GAO interviewed DOD, VA, and researchers affiliated with published articles, as well as other stakeholders, including officials with the Undersea and Hyperbaric Medical Society. GAO also interviewed officials from the Food and Drug Administration about the process to approve HBO_2 therapy for the treatment of TBI and PTSD.

GAO provided a draft of this report to DOD, VA, and the Department of Health and Human Services. Each of the departments provided technical comments, which GAO incorporated, as appropriate.

View GAO-16-154. For more information, contact Debra A. Draper at (202) 512-7114 or draperd@gao.gov.

What GAO Found

GAO identified 32 peer-reviewed, published articles on research about the use of hyperbaric oxygen (HBO_2) therapy to treat traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD), most of which were focused solely on TBI (29 articles). The 32 articles consisted of 7 case reports (reports on the treatment of individuals), 10 literature reviews (reviews of studies), and 15 articles on interventional studies or clinical trials, which provide the strongest clinical evidence about a treatment. Three of the 15 articles on interventional studies or clinical trials focused on the safety of HBO_2 therapy for treating TBI and concluded that it is safe. The other 12 articles described the effectiveness of HBO_2 therapy in treating TBI. Four of these articles (two on severe TBI and two that did not specify severity) reported that HBO_2 therapy was effective. The remaining eight articles focused on mild TBI—six concluded that it was not effective and two concluded that it was.

The six articles that concluded HBO_2 therapy was not effective in treating mild TBI were based on three studies funded by the Department of Defense (DOD) with collaboration from the Department of Veterans Affairs (VA) and others. Each of the DOD-funded studies 1) was randomized—participants were randomly assigned to clinical trial groups, 2) was double-blinded—neither researchers nor participants knew who was assigned to which group, and 3) included a sham control group—participants received a procedure that was similar to HBO_2 therapy but lacked certain components of the intervention. However, there is no standard design for sham control groups in HBO_2 therapy, and in each of the DOD-funded studies the approach varied. The authors of the six articles based on these studies concluded that HBO_2 therapy was not effective in treating mild TBI because participants in the sham control and treatment groups had similar outcomes. Although both groups showed improvement, the researchers concluded that this was likely due to other factors, such as a placebo effect. Researchers not affiliated with the DOD-funded studies have raised concerns about whether the sham control groups received a placebo or a therapeutic treatment. In a published editorial, researchers affiliated with one of the DOD-funded studies acknowledged the challenges associated with designing a sham control group and stated that additional research would be needed to determine whether these participants actually received a therapeutic benefit. DOD officials told us that studying the long-term effects of the treatment also would help confirm whether the sham control groups' improvements should be attributed to a placebo effect.

The two articles that concluded that HBO_2 therapy was effective in treating mild TBI were based on studies that were designed differently than the DOD-funded studies. DOD and VA researchers told GAO that the studies related to these articles did not have the same methodological rigor as the DOD-funded studies because they did not have design features such as sham control groups, which help ensure the validity of a study's findings. The researchers for one of these two studies noted in their article that they did not use a sham control group because it was difficult to ensure that participants would receive a non-therapeutic treatment. Researchers for the other study noted in their article that a sham control group was not used because this was preliminary work, and further work would be needed to confirm the findings.

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Abbreviations

ATA	atmosphere absolute
DOD	Department of Defense
FDA	Food and Drug Administration
HBO_2	hyperbaric oxygen
IND	investigational new drug
NIH	National Institutes of Health
PTSD	post-traumatic stress disorder
TBI	traumatic brain injury
VA	Department of Veterans Affairs

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U.S. GOVERNMENT ACCOUNTABILITY OFFICE
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Congressional Committees

Traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) are signature wounds for servicemembers returning from the conflicts in Iraq and Afghanistan. TBI is a traumatically induced structural injury or physiological disruption of brain function resulting from an external force that is indicated by clinical signs, such as confusion, disorientation, or memory loss.[1] PTSD is a trauma- and stressor-related disorder that can develop after an extremely stressful event, such as the threat of death or serious injury. The nature of the current conflicts—particularly the widespread use of improvised explosive devices—increases the likelihood that active duty servicemembers will be exposed to incidents, such as blasts, that can result in these conditions.[2]

TBIs vary greatly in terms of severity. Mild TBIs are commonly referred to as concussions and may be difficult to detect because of the absence of a visible injury, while severe cases may involve an extended period of unconsciousness or amnesia after the injury. The health implications of TBI, which can be dependent on the severity of the injury, may include a wide range of physical, mental, social, and emotional symptoms. The majority of TBIs overall, in the military and the general population, have been classified as mild. Most individuals with mild TBI recover quickly, within a matter of hours to days.

Symptoms of PTSD include insomnia, intense anxiety, nightmares, and difficulties coping with work, family, and social relationships, among others. PTSD can also be associated with substance abuse, severe

[1]TBI is indicated by new onset or worsening of at least one of the following clinical signs immediately following the event: any alteration in mental status (e.g. confusion, disorientation, slowed thinking, etc.); any loss of memory for events immediately before or after the injury; and any period of loss of or a decreased level of consciousness, observed or self-reported. External forces may include any of the following events: the head being struck by an object, the head striking the object, the brain undergoing a movement without direct external trauma to the head, or forces generated from events such as a blast or explosion, including penetrating injuries.

[2]According to Department of Defense (DOD) officials, the majority of TBIs for servicemembers occur in the United States from injuries that are not combat related.

depression, and suicide. Experts believe that early identification and treatment of PTSD-related symptoms may lessen the severity of the condition and improve the overall quality of life for servicemembers. Studies have found that one-third or more of servicemembers with mild TBI also have PTSD.[3]

Treatment for mild TBIs may consist of therapies, such as physical and cognitive rest, while treatment for moderate and severe TBIs is usually focused on managing the initial injury to the brain followed by other therapies. To treat PTSD, patients are often prescribed various psychotropic drugs to ease their symptoms, although these drugs may have negative side effects. As an alternative to these treatments, some researchers have studied the use of hyperbaric oxygen (HBO_2) therapy to treat TBI or PTSD, which delivers higher-than-normal levels of oxygen to the body inside of a hyperbaric chamber and is hypothesized to promote healing, reduce brain damage, and improve long-term outcomes. Some of these researchers have reported positive results with this therapy. In contrast, research conducted by the Department of Defense (DOD) and the Department of Veterans Affairs (VA) has found that it does not appear to be effective in treating mild TBI based on their research to date. Additionally, to date, the Food and Drug Administration (FDA) has not approved this therapy as a treatment for TBI or PTSD.[4]

The Joint Explanatory Statement accompanying the Consolidated and Further Continuing Appropriations Act, 2015, included a provision for us to review the use of HBO_2 therapy to treat TBI and PTSD. In this report, we identify and describe published research on the use of this therapy in the treatment of these conditions.

To identify and describe published research on the use of HBO_2 therapy in the treatment of TBI or PTSD, we conducted a literature review and interviewed relevant federal officials, researchers, and other stakeholders about their work related to this therapy for these conditions. For the literature review, we searched for relevant articles published in peer-reviewed journals during the most recent 10-year period, from January 1,

[3]According to DOD officials, some studies have reported that up to 60 to 70 percent of veterans with mild TBI also have PTSD.

[4]FDA is the agency responsible for protecting the public health by assuring, among other things, the safety and efficacy of drugs, biological products, and medical devices.

2005 through April 6, 2015, and we identified and reviewed 32 articles that met our inclusion criteria.[5] We examined the methodologies for each of these articles and determined that they were sufficiently reliable for the purposes of our report. (For more details about the methodology of our literature review and a list of the articles we reviewed, see appendix I.) We interviewed DOD and VA officials and researchers about their completed and ongoing research on the effectiveness of HBO_2 therapy for the treatment of TBI or PTSD, including their viewpoints on research completed by others. We also reviewed VA's literature review on this topic, as well as a literature review that was prepared for DOD by a contractor.[6] In addition, we interviewed DOD's literature-review contractor and other researchers, including researchers affiliated with published articles we identified; and other stakeholders, including officials with the Undersea and Hyperbaric Medical Society and the American Association of Hyperbaric Awareness.[7] We also interviewed FDA officials about the process to approve HBO_2 therapy for the treatment of TBI or PTSD. Finally, we obtained information from the National Institutes of Health (NIH) about ongoing clinical studies on the use of HBO_2 therapy for the treatment of TBI or PTSD included in the database it maintains, ClinicalTrials.gov, the world's largest registry of publicly and privately supported clinical studies. Specifically, we obtained information about clinical studies with start dates between January 1, 2005 and July 22, 2015 that had not completed data collection. We determined that the data in the ClinicalTrials.gov registry was sufficiently reliable for the purposes of this report based on information from NIH officials about the procedures in place to ensure the quality and completeness of these data. Information about ongoing research is contained in appendix II.

[5]We chose this period because federal officials became aware of increased rates of TBI among active duty servicemembers in the mid-2000s.

[6]In July 2014, DOD hired the Samueli Institute, a non-profit research institute, to conduct a systematic literature review of the efficacy of HBO_2 therapy for patients with TBI, and to develop conclusions based on the current state of the evidence for its application as well as next steps for researching its effectiveness.

[7]The Undersea and Hyperbaric Medical Society is an international scientific organization that was founded in 1967 to foster exchange of data on the physiology and medicine of commercial and military diving. Over the years, its focus has expanded to include HBO_2 therapy, and it has become an important source for scientific information for hyperbaric medicine.

We conducted this performance audit from May 2015 to December 2015 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Background

TBI and PTSD

TBI can be classified as mild, moderate, or severe based on specific criteria, such as the length of time an individual is unconscious following their injury. For example, an individual would meet the criteria for mild TBI if they suffered a loss of consciousness for 30 minutes or less. Similarly, an individual would meet the criteria for moderate TBI if they lost consciousness for more than 30 minutes and for severe TBI if they lost consciousness for more than 24 hours. (See table 1.)

Table 1: Classification of Traumatic Brain Injury (TBI) Severity

Criteria	Mild	Moderate	Severe
Structural imaging[a]	Normal[b]	Normal or abnormal	Normal or abnormal
Loss of consciousness	0—30 minutes	>30 minutes and <24 hours	>24 hours
Alteration of consciousness or mental state[c]	a moment up to 24 hours	>24 hours, severity based on other criteria	>24 hours, severity based on other criteria
Post-traumatic amnesia	0—1 day	>1 and <7 days	>7 days
Glasgow Coma Scale (best available score in first 24 hours)[d]	13—15	9—12	<9

Source: Departments of Veterans Affairs and Defense. | GAO-16-154

[a]Structural imaging refers to the structure of the brain as viewed through magnetic resonance imaging, computed tomography scanning, or other technologies.

[b]Structural imaging is not always indicated for patients with mild TBIs.

[c]Alteration of mental state must be immediately related to the head trauma. Typical symptoms would be looking and feeling dazed and uncertain of what is happening, confusion, difficulty thinking clearly or responding appropriately to mental status questions, and being unable to describe events immediately before or after the trauma event.

[d]The Glasgow Coma Scale was designed to and is used to assess the depth and duration of the coma and impaired consciousness. This scale helps to gauge the impact of a wide variety of conditions, such as acute brain damage due to traumatic injuries, vascular injuries or both. As of April 2015, DOD's definition of TBI did not include the Glasgow Coma Scale.

Early detection of injury is critical in the management of TBI patients. The diagnosis of moderate and severe TBI usually occurs in a timely manner due to the visible nature of the head injury, as well as the duration of symptoms, such as memory loss. Identification of mild TBI, also known as a concussion, can be challenging because there may be no visible head injury, and symptoms may be minimal and brief. In addition, in the combat theater, a mild TBI may not be identified if it occurs at the same time as other combat injuries that are more visible or life-threatening, such as orthopedic injuries or open wounds. Furthermore, some of the symptoms of mild TBI, which account for the majority of these injuries in the military, are similar to those associated with other conditions, such as PTSD.

Individuals sustaining mild TBIs often report physical, cognitive, and emotional or behavioral symptoms referred to collectively as postconcussion symptoms. The most commonly reported postconcussion symptoms are headache, dizziness, decreased concentration, memory problems, irritability, fatigue, visual disturbances, sensitivity to noise, judgment problems, depression, and anxiety. Although the majority of individuals with mild TBI have symptoms that resolve within 1 month, some symptoms may persist for months to years following injury, potentially becoming permanent and causing disability. When these symptoms are persistent, they are often referred to as postconcussion syndrome or persistent postconcussion symptoms.

PTSD can develop following exposure to life-threatening events, natural disasters, terrorist incidents, serious accidents, or violent personal assaults and may have a delayed onset, which is described as a clinically significant presentation of symptoms at least 6 months after exposure to trauma. Individuals diagnosed with PTSD may experience problems sleeping, maintaining relationships, and returning to their previous civilian lives. They may also suffer from other ailments, such as depression and substance abuse. PTSD is one of the most prevalent mental disorders arising from combat.

HBO_2 Therapy

HBO_2 therapy is a medical procedure which results in higher-than-normal levels of oxygen in the body's blood and tissues. It is a first-line therapy for medical emergencies related to decompression sickness, air or gas embolism, and carbon monoxide poisoning. It can also be used as an adjunctive (additional) therapy to surgical or pharmacologic interventions. As defined by the Undersea and Hyperbaric Medical Society, hyperbaric oxygen is an intervention that involves breathing near 100 percent oxygen intermittently while inside a sealed chamber that is pressurized to greater

than sea level pressure (1 atmosphere absolute [ATA]). For clinical purposes, the Undersea and Hyperbaric Medical Society has said that the pressure must equal or exceed 1.4 ATA while breathing near 100 percent oxygen.[8] In contrast to the oxygen levels used in HBO_2 therapy, the ambient air that we breathe contains 20.9 percent oxygen.

Currently, FDA has not approved HBO_2 therapy as a treatment for TBI and PTSD, although it has approved it for treating other conditions. Similarly, DOD and VA have adopted, and the Undersea and Hyperbaric Medical Society has endorsed, the use of HBO_2 therapy for a variety of indications (diseases or medical conditions), but not as a treatment for TBI and PTSD. (See table 2.)

[8]See the Undersea and Hyperbaric Medical Society, *Hyperbaric Oxygen Therapy Indications*, *13th Edition,* 2014, as well as its website accessed on August 19, 2015 at https://www.uhms.org/resources/hbo-indications.html. Prior to the 13th edition, the definition of HBO_2 for clinical purposes was "100 percent oxygen" instead of "near 100 percent oxygen" *Hyperbaric Oxygen Therapy Indications, 12th Edition*, 2008. However, the latest edition remained consistent that pressurization for clinical purposes should be 1.4 ATA or higher.

Table 2: Medical Indications for Hyperbaric Oxygen (HBO_2) Therapy in the United States Approved by the Food and Drug Administration (FDA) or Adopted or Endorsed by Others

Medical indications	FDA	Department of Defense (DOD)[a]	Department of Veterans Affairs(VA)	Undersea and Hyperbaric Medical Society
Acute thermal burn injury	√		√	√
Air or gas embolism	√	√	√	√
Arterial insufficiencies (central retinal artery occlusion or enhancement of healing in selected problem wounds)	√	√	√	√
Carbon monoxide poisoning or carbon monoxide poisoning complicated by cyanide poisoning	√	√	√	√
Clostridial myositis and myonecrosis (gas gangrene)	√	√	√	√
Crush injury, compartment syndrome and other acute traumatic ischemias	√	√	√	√
Compromised skin graphs and flaps	√	√	√	√
Decompression sickness	√	√	√	√
Delayed radiation injury (soft tissue and bony necrosis)	√	√	√	√
Exceptional blood loss (anemia)	√	√	√	√
Idiopathic sudden sensorineural hearing loss				√
Intracranial abscess	√		√	√
Necrotizing soft tissue infections	√		√	√
Osteomyelitis (refractory)	√	√	√	√

Source: FDA, DOD, VA, and the Undersea and Hyperbaric Medical Society. | GAO-16-154

Notes: There are some small variations in the names of the approved, adopted, or endorsed indications by organizations.

[a]According to TRICARE (DOD's health care program) policy, DOD may cover HBO_2 for other indications when documented by other reliable evidence as safe, effective, and comparable or superior to standard care.

FDA Drug Approval and Device Approval/ Clearance Process

FDA approves drugs and approves/clears devices for specific indications (diseases or medical conditions). However, it does not generally prevent healthcare practitioners' use or prescribing of approved or cleared drugs/devices for indications for which the drugs/devices have not been approved or cleared. FDA has approved/cleared both the drug (oxygen) and the device (hyperbaric chamber) used in HBO_2 therapy for certain medical uses, such as treating decompression sickness suffered by divers. As described by FDA officials, in order for HBO_2 therapy and the hyperbaric oxygen chamber to be marketed for new indications, such as

TBI or PTSD, sponsors would be required to submit a new marketing application or applications to support the new indications.[9] Such submissions could be made in one of two ways: 1) the sponsor could submit one marketing application to FDA's Center for Drug Evaluation and Research for both the drug and the device; or 2) the sponsor could submit a new drug application to FDA's Center for Drug Evaluation and Research to add the new oxygen indication for the drug and a device premarket submission to FDA's Center for Devices and Radiological Health to add the new indication for existing hyperbaric oxygen chambers.[10]

Typically before a marketing application submission, the sponsor meets with FDA to discuss the most appropriate investigational studies and the details of the regulatory process. If existing literature and data are available to address the scientific and technical questions, it might be possible to submit this information only, and new investigational studies might not be needed. If new investigational studies are needed, an investigational new drug (IND) application would be used. The IND would include information on both the drug and the device. The IND must also include a "proposed indication(s) for use" section that explains what the drug (or drug-device combination product) does and the clinical condition and population for which it is intended. The IND sponsor has overall responsibility for the conduct of clinical studies that would support use for the proposed indication. Typically, the investigational process is iterative and begins with early studies that focus on safety and dosing. Later studies generally focus on safety and effectiveness of the product.

[9]A sponsor is typically the drug or device manufacturer that submits the application.

[10]FDA's Center for Drug Evaluation and Research regulates over-the-counter and prescription drugs, including biological therapeutics and generic drugs. FDA's Center for Devices and Radiological Health is responsible for the premarket approval of all medical devices, as well as overseeing the manufacturing, performance and safety of these devices. FDA's clearance of a device for a specific use under the "510(k) process (a premarket review process set forth in section 510(k) of the Federal Food, Drug, and Cosmetic Act) means FDA determined that 1) the device has the same intended use as a predicate (a device already on the market) and (2) has the same technological characteristics as the predicate or has different technological characteristics but the device is at least as safe and effective as a predicate and does not raise different questions of safety and effectiveness than the predicate. Devices that do not qualify for premarket review under the 510(k) process (e.g. when there is no qualifying predicate device) would need to submit the application under a different Center for Devices and Radiological Health regulatory pathway.

When the applicant completes the investigational studies and submits the necessary marketing application for review, FDA first determines whether the submission is complete and provides the information necessary for review.[11] For example, the submission would provide information regarding the product description, proposed indications and potential clinical benefits, as well as the data needed to support approval or clearance, labeling, dose of the drug, and device instructions for use. FDA reviews the marketing application to determine such things as whether 1) the drug-device combination is safe and effective for its proposed use, which is answered, at least in part, by whether the benefits of the treatment outweigh its risks; 2) the proposed labeling meets the applicable regulatory requirements; 3) the methods used to manufacture the drug are adequate to preserve the drug's identity, strength, quality, and purity; and 4) the methods used to maintain device functionality and performance are acceptable. If two marketing applications are used as in the second option noted above, FDA would generally issue the marketing authorizations concurrently when they are approved.

Published Research on the Use of HBO_2 Therapy to Treat TBI and PTSD is Primarily Focused on TBI; Conclusions on Effectiveness for Mild TBI Differ

Most Published HBO_2 Therapy Research Is Focused on the Safety and Effectiveness of Treating TBI with Few Studies on PTSD

Most of the 32 peer-reviewed, published articles that we identified examined the use of HBO_2 therapy for treating TBI: 29 focused solely on TBI, 2 focused on both TBI and PTSD, and 1 focused solely on PTSD. The 32 articles we identified included 7 case reports, 10 literature reviews, and 15 articles on interventional studies or clinical trials.

[11]Sponsors may submit more than one application as noted above.

- Case reports are collections of reports on the treatment of individual patients. Six of the seven case reports we reviewed found that the patients with TBI (mild, moderate, severe, or not specified) or PTSD improved after treatment. The remaining case report noted safety issues to consider when treating TBI patients with cranial fractures.

- Literature reviews use a search to identify studies on a specific clinical topic. Of the 10 literature reviews we identified, 1 concluded based on the articles it had identified that HBO_2 therapy had positive effects when used to treat severe TBI, 1 concluded that the therapy can be delivered with relative safety for severe TBI, and 8 noted that further research was needed to determine if this treatment was effective.

- Interventional studies or clinical trials assign participants to receive one or more interventions (or no intervention) so that researchers can evaluate the effects of the interventions on health-related outcomes. This type of research provides the strongest clinical evidence on whether the intervention has an effect on the disease because these studies are designed to isolate the effect of the intervention in question. Of the 15 articles we reviewed on interventional studies or clinical trials, 3 focused on the safety of HBO_2 therapy for treating TBI (severe and not specified), and all 3 concluded that the therapy is safe. The remaining 12 articles evaluated the effectiveness of HBO_2 therapy in treating TBI: 8 focused on mild TBI, 2 focused on severe TBI, and the remaining 2 articles did not specify severity.[12] The 8 articles on mild TBI had differing conclusions on the effectiveness of HBO_2 therapy, while the other 4 articles (two on severe TBI and two that did not specify severity) reported that this therapy was an effective treatment for these conditions.

(For more detailed information about the articles and their conclusions, see appendix III for case reports, appendix IV for literature reviews, and appendix V for interventional studies or clinical trials.)

[12]Based on our review of the articles, we determined that 4 of the 12 articles related to the same study. Researchers used the data to produce more than one published article, each of which focused on different aspects of the study.

Articles about the Effectiveness of HBO_2 Therapy for Treating Mild TBI Report Different Conclusions

The eight articles on interventional studies or clinical trials that were focused on treating mild TBI had different conclusions—six articles concluded that it was not effective and two concluded that it was. The six articles that concluded HBO_2 therapy was not effective were based on three studies funded by DOD with collaboration from VA and others (referred to in this report as DOD-funded studies).[13] Each of the three studies was affiliated with a branch of military service—Army, Navy, or Air Force. The remaining two articles were based on two studies conducted by researchers in Israel and the United States.

The differences in the articles' conclusions about the effectiveness of HBO_2 therapy for treating mild TBI are based, in part, on methodological differences, as well as differences in researchers' interpretations of the studies' results. All of the DOD-funded studies were randomized, double-blinded, and included a sham control group in which participants received a procedure that is similar to the HBO_2 therapy being studied.[14] For a sham control group in HBO_2 therapy studies, some atmospheric pressure within the hyperbaric chamber is required for participants to perceive they are receiving treatment. However, there is no standard sham control group design for HBO_2 therapy, and in each of the DOD-funded studies the approach varied. (See table 3.) The authors of the six articles based on these studies concluded that HBO_2 therapy was not effective in treating mild TBI and related symptoms because participants in the sham control and treatment groups had similar outcomes. Although both groups of participants showed improvement, the authors concluded that the improvement was likely attributable to other factors, such as a placebo effect, and not to HBO_2 therapy.[15] DOD officials and researchers involved with the studies told us that they believe some improvements were due to factors, such as being away from home and everyday stress.

[13]These studies were funded by DOD and conducted by researchers affiliated with DOD, VA, universities, and other organizations.

[14]Randomization is a strategy in which participants are assigned to groups of a clinical trial by chance. Blinding of a study is a design strategy in which one or more parties involved with the trial, such as the researcher, participant or both, do not know which participants have been assigned which interventions. Types of blinding include: none, single blinded, or double blinded. A sham control group receives a treatment or procedure under investigation, but is lacking the component(s) of the intervention being studied.

[15]The placebo effect is a change in symptoms for patients who unknowingly receive a treatment that does not contain the therapy or therapies being studied.

Table 3: Design of the Sham Control and Treatment Groups for DOD-Funded Studies by Service Branch

Service branch	Design of sham control group	Design of treatment group(s)
Air Force	Room air (about 21% oxygen) at 1.3 ATA[a]	100% oxygen at 2.4 ATA
Army	Room air (about 21% oxygen) at 1.2 ATA	100% oxygen at 1.5 ATA[b]
Navy	10.5% oxygen at 2.0 ATA[c]	75% oxygen at 2.0 ATA[d] 100% oxygen at 2.0 ATA

Source: GAO review of published articles. | GAO-16-154

[a]ATA refers to atmosphere absolute.1.0 ATA is equal to pressure at sea level.

[b]Some of the participants in this study were also placed in a third group that received standard care for mild TBI, but did not receive supplemental hyperbaric oxygen therapy.

[c]This is the oxygen breathing equivalent of room air at sea level.

[d]This is the oxygen breathing equivalent of 100 percent oxygen at 1.5 ATA.

However, other researchers (who did not participate in the DOD-funded studies) have stated that these studies demonstrate that HBO_2 therapy is effective in treating mild TBI since both the sham control and treatment groups showed improvement. These other researchers have raised concerns about the methodology of the DOD-funded studies, which are related to whether the sham control groups received a true sham treatment (a placebo) rather than HBO_2 therapy.[16] The researchers who conducted the DOD-funded studies considered the Undersea and Hyperbaric Medical Society's clinical definition of HBO_2 therapy (near 100 percent oxygen at a pressure greater than or equal to 1.4 ATA) when designing the sham control groups for their studies to ensure that participants in these groups received a lower pressure or a much lower concentration of oxygen than would be considered therapeutic. A researcher not associated with the DOD-funded studies stated that the Undersea and Hyperbaric Medical Society definition is arbitrary because it implies that there is no therapeutic effect for a patient who receives pressure less than 1.4 ATA and less than 100 percent oxygen.[17] Further,

[16]A researcher who did not participate in the DOD-funded studies also expressed concerns about the statistical analyses used in the DOD-funded research. For example, the researcher told us that in one of articles based on a DOD-funded study (Navy), the authors did not compare patients' test scores for cognitive, balance, or fine motor deficits prior to receiving HBO_2 therapy to test scores obtained after receiving this therapy. This researcher stated that without this comparison, it is impossible to draw conclusions on the effects of HBO_2 therapy from this study.

[17]Harch, P. G., "Hyperbaric Oxygen in Chronic Traumatic Brain: Oxygen, Pressure, and Gene Therapy" Medical Gas Research (2015) 5-9.

other researchers not affiliated with the DOD-funded studies have reported that hyperbaric treatments at 1.2 ATA (without increased oxygen levels), which was used as the sham treatment in one DOD-funded study, substantially increase the amount of dissolved oxygen in the blood and simultaneously induces other physiological changes.[18] As a result, these other researchers stated that the sham control group's treatment does not represent a true sham or placebo, and participants' improvement shows that even a small increase in pressure is an effective treatment.

In a published editorial, the researchers who conducted the DOD-funded study that used a sham control group with hyperbaric treatments at 1.2 ATA responded to these concerns by reporting that they recognize that the sham treatment may have caused physiologic effects from slight increases in oxygen, nitrogen, and direct pressure, as well as a variety of other effects.[19] They added that the study was not designed to separate these effects, but rather to show a benefit of HBO_2 therapy beyond these effects, which it failed to do. Their article also acknowledged the challenges associated with designing a sham control group as participants must feel some pressure to mask the intervention. They reported that the DOD-funded studies varied the design of the sham control groups so that the results could be examined collectively and that the oxygen dose used in the sham control groups would never be considered therapeutic. Furthermore, their article stated that additional research would be needed to determine if there was an actual therapeutic benefit of higher pressure without an increased oxygen concentration. They also reported that what may be more important than whether the observed benefits are due to factors, such as placebo effects, is whether these benefits are durable. One of the researchers involved in the DOD-funded studies also told us that they studied the results for participants in the sham control and treatment groups 3 months after they received HBO_2 therapy, and found it was not effective because the initial improvements identified after the treatments were not sustained. Nonetheless, DOD officials told us that there have been no studies completed on the long-term effects of the treatment, and such studies

[18]Marios, P., A. Mukherjee, L. Ballaz, "Hyperbaric Oxygen Treatment for Persistent Postconcussion Symptoms-A Placebo Effect?" *JAMA Internal Medicine*, vol. 175, no. 7 (2015) 1239-1240.

[19]Miller, R.S., L.K. Weaver, L.A. Brenner, "Hyperbaric Oxygen Treatment for Persistent Postconcussion Symptoms-A Placebo Effect?" *JAMA Internal Medicine*, vol. 175, no. 7 (2015) 1240-1241.

would help confirm whether the sham control groups' improvements should be attributed to placebo effects or other factors.

The remaining two (of eight) articles on mild TBI, which concluded that HBO_2 therapy is effective, used different methodologies than the DOD-funded studies. The research conducted in Israel was a prospective study that was single-blinded and used a crossover control group.[20] The study conducted in the United States was not blinded and did not use a control group. DOD and VA researchers and other subject matter experts told us that these studies were not designed with the same methodological rigor as the DOD-funded studies on mild TBI because they were not blinded, randomized clinical trials, and they did not use sham control groups—qualities that help ensure the validity of a study's findings. The group of researchers in Israel noted in their article that they did not use a sham control group because it was difficult to design a treatment for the control group that would not be considered therapeutic. The researchers for the other study that was conducted in the United States noted in their article that a sham control group was not used because this was preliminary work, and further work would be needed to confirm the study's findings.

[20]A crossover design describes a clinical trial in which groups of participants receive interventions in a particular order. For example, in the Israeli study, the crossover design involved two groups of participants receiving either HBO_2 therapy or no treatment for TBI. One group received the therapy during the initial phase of the trial, followed by no treatment during a later phase. The other group received no treatment during the initial phase, followed by the therapy during a later phase. During the study, participants "crossed over" to the other intervention. All participants received HBO_2 therapy and no treatment at some point during the study, but in a different order, depending on the group to which they are assigned. Further, the practitioners evaluating the results of this study did not know, or were blinded, to the participants' group assignments.

VA and DOD Also Conducted Literature Reviews That Incorporated Recent Published Research on the Effectiveness of HBO_2 Therapy to Treat TBI

In addition to the 10 published literature review articles we identified, both VA and DOD conducted their own literature reviews on the effectiveness of HBO_2 therapy to treat TBI (all severities); VA's literature review also included PTSD. In developing the department's policy on the use of HBO_2 therapy for TBI and PTSD, VA produced a report in 2010 that summarized information from published, peer-reviewed research on the appropriate clinical use of this therapy for TBI and PTSD.[21] VA's report concluded that high quality, well-designed research is needed to determine the efficacy and effectiveness of HBO_2 therapy for both of these conditions.[22] In 2014, VA updated its report to include articles published between January 1, 2010 and January 17, 2014. In its updated report, VA concluded that none of the well-designed studies it reviewed, including the DOD-funded studies, demonstrated that HBO_2 therapy was effective for the treatment of TBI.[23] Further, the report noted that the 2013 Israeli study—which found the treatment to be effective for improving cognitive performance and self-perceived quality of life—did not have adequate controls, such as a sham control group.[24]

In July 2014, DOD hired a contractor, the Samueli Institute, to conduct a systematic literature review on the efficacy of HBO_2 therapy for patients with TBI and to develop conclusions based on the current state of the evidence for its application, as well as determine next steps for researching its effectiveness. The report prepared by the contractor reviewed all available literature through the end of 2014 and covered all

[21]In 2009, VA officials requested that VA's Technology Assessment Advisory Group examine the use of HBO_2 therapy to treat TBI and PTSD. To conduct this assessment, the advisory group examined published, peer-reviewed evidence, input from VA's Technology Assessment Program and Clinical Expert Panels, and a utilization and cost analysis.

[22]For both VA white papers, see http://www.indianapolis.va.gov/VERC/White_Papers/Hyperbaric%20oxygen%20therapy%20for%20TBI%20and%20PTSD..pdf [Accessed on October 13, 2015].

[23]The updated review of literature in 2014 also reviewed literature on the use of HBO_2 therapy to treat stroke. The review concluded that there was no new scientific evidence indicating that HBO_2 therapy is an effective treatment for either TBI or stroke.

[24]While the paper did not explicitly define well-designed, the following limitations were noted: 1) the study did not incorporate a valid sham control group, 2) the participants and researchers were not effectively blinded about HBO_2 therapy, and 3) the outcome measures were susceptible to improving based upon the participants' expectations as to whether they should improve or not. The paper noted that the last criticism could explain many of the reported improvements in cognitive performance.

severities of TBI.[25] With respect to mild TBI, it noted that the improvements in outcomes shown within the groups receiving HBO_2 therapy, as well as the sham treatment, in the DOD-funded studies cannot be ignored. It also discussed the debate on what constitutes a true sham for HBO_2 therapy. Specifically, the report stated that a true sham treatment may have to be done with normal atmospheric pressure and that more research is needed to be confident that a sham is not a therapeutic treatment. The report concluded that further research, such as conducting studies comparing other types of interventions to HBO_2 therapy for TBI, should be considered in order to resolve the controversy surrounding this field, but only if these studies can be designed without methodological flaws.

Agency Comments

We provided a draft of this report to DOD, the Department of Health and Human Services, and VA for comment. Each of the departments provided technical comments, which we incorporated as appropriate. VA also provided general comments about the extent to which we cover research on HBO_2 therapy to treat PTSD. As noted in our report, PTSD was only included in three articles that we reviewed, and as a result, our description of research on HBO_2 therapy to treat PTSD was limited. DOD's comments are reprinted in appendix VI, and VA's comments are reprinted in appendix VII. The Department of Health and Human Services did not provide a formal response letter.

We are sending copies of this report to the Secretaries of Defense, Health and Human Services, Veterans Affairs, and appropriate congressional committees. In addition, the report will be available at no charge on the GAO website at http://www.gao.gov.

If you or your staff have any questions about this report, please contact me at (202) 512-7114 or draperd@gao.gov. Contact points for our Offices

[25]DOD officials told us that the report would be publicly available in 2016.

of Congressional Relations and Public Affairs may be found on the last page of this report. Major contributors to this report are listed in appendix VIII.

Debra A. Draper
Director, Health Care

List of Committees

The Honorable John McCain
Chairman
The Honorable Jack Reed
Ranking Member
Committee on Armed Services
United States Senate

The Honorable Thad Cochran
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The Honorable Richard J. Durbin
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Chairman
The Honorable Peter J. Visclosky
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Subcommittee on Defense
Committee on Appropriations
House of Representatives

Appendix I: Literature Review Methodology and Bibliography

To identify and describe published research on the use of hyperbaric oxygen (HBO_2) therapy in the treatment of traumatic brain injury (TBI) or post-traumatic stress disorder (PTSD), we conducted a literature search for relevant articles published during the most recent 10-year period, from January 1, 2005 through April 6, 2015.[1] Our librarian searched more than 30 databases for research published in relevant peer-reviewed and industry journals including Academic One File, ArticleFirst, BIOSIS Previews, CINAHL, Embase, MEDLINE, NTIS: National Technical Information Service , PILOTS: Published International Literature on Traumatic Stress, PsycINFO, and WorldCat. Key search terms included various combinations of "hyperbaric oxygen," "hyperbaric oxygen therapy," "hyperbaric oxygen treatment," "traumatic brain injury," and "post-traumatic stress disorder." From all database sources, 230 abstracts were identified.

We first reviewed the abstracts for each of these articles for relevancy in determining the effectiveness of HBO_2 therapy in treating TBI or PTSD.[2] For those abstracts we found relevant, we obtained and reviewed the full article and excluded those for which the research (1) was an editorial submission; (2) studied animals; or (3) included children. After excluding these articles, duplicates, and those only available in a foreign language, 32 articles remained. Articles were then categorized as a case report, literature review, or interventional study or clinical trial.[3] We identified 7 case reports, 10 literature reviews, and 15 interventional studies or clinical trials, which are listed below (chronologically, then alphabetically by first author, and for the interventional studies or clinical trials, by

[1]We chose this period because federal officials became aware of increased rates of TBI among active duty servicemembers in the mid-2000s.

[2]We reviewed the abstracts and did not obtain full articles if TBI or PTSD was not included in the research, HBO_2 therapy was not at least one treatment used in the research, the abstract was from a conference and not available in a full article, or the abstract was from a book.

[3]Case reports consist of collections of reports on the treatment of individual patients or a report on a single patient. For the purposes of our work, if a case report examined more than one patient it would describe each of the cases individually. Literature reviews focus on a clinical topic and answer a specific question. An interventional study or clinical trial is a clinical study in which participants are assigned to receive one or more interventions (or no intervention) so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes. The assignments are determined by the study protocol. Participants receiving an intervention may receive diagnostic, therapeutic, or other types of interventions.

severity of TBI and then by study location). As part of our work, we examined the methodologies of each of these studies and determined that they were sufficiently reliable for the purposes of our report.

Case Reports vs (7 Articles)

Hardy, P.G., K.M. Johnston, L. DeBeaumont, D.L. Montgomery, J. M., Lecomete, J.P. Soucy, D. Bourbonnais, and M. Lassonde. “Pilot Case Study of the Therapeutic Potential of Hyperbaric Oxygen Therapy on Chronic Brain Injury.” *Journal of Neurological Sciences*, vol. 253 (2007).

Harch, P., E.F. Fogarty, P.K. Staab, and K. Van Meter. “Low Pressure Hyperbaric Oxygen Therapy and SPECT Brain Imaging in the Treatment of Blast-Induced Chronic Traumatic Brain Injury (Post-Concussion Syndrome) and Post Traumatic Stress Disorder: A Case Report.” *Cases Journal*, vol. 2 (2009).

Wright, Col. J,K., E. Zant, K. Groom, R.E. Schlegel, and K. Gilliland. “Case Report Treatment of Mild Traumatic Brain Injury with Hyperbaric Oxygen*.” Undersea & Hyperbaric Medicine*, vol. 36, no. 6 (2009).

Eovaldi, B., and C. Zanetti. “Hyperbaric Oxygen Ameliorates Worsening Signs and Symptoms of Post-Traumatic Stress Disorder.” *Neuropsychiatric Disease and Treatment*, vol. 6 (2010).

Lv, L.Q., L.J. Hou, M.K. Yu, X.H. Ding, X.Q. Qi, and Y.C. Lu. “Hyperbaric Oxygen Therapy in the Management of Paroxysmal Sympathetic Hyperactivity after Severe Traumatic Brain Injury: A Report of 6 Cases.” *Arch. Phys. Med. Rehabil.*, vol. 92 (2011).

Stoller, K. “Hyperbaric Oxygen Therapy (1.5 ATA) in Treating Sports Related TBI/CTE: Two Case Reports.” *Medical Gas Research*, vol. 1 (2011).

Lee, L.C., F.K. Lieu, Y.H. Chen, T.H. Hung, and S.F. Chen. “Tension Pneumocephalus as a Complication of Hyperbaric Oxygen Therapy in a Patient with Chronic Traumatic Brain Injury.” *American Journal of Physical Medicine & Rehabilitation*, vol. 91, no. 6 (2012).

Literature Reviews (10 Articles)

Adamides, A.A., C.D. Winter, P.M. Lewis, D.J. Cooper, T. Kossmann, and J.V. Rosenfeld. “Current Controversies in the Management of Patients with Severe Traumatic Brain Injury.” *ANZ. J. Surg*., vol. 76 (2006).

Bennett, M.H., B.E. Trytko, and B. Jonker. “A Systematic Review of the Use of Hyperbaric Oxygen Therapy in the Treatment of Acute Traumatic Brain Injury.” *Diving and Hyperbaric Medicine*, vol. 36, no. 1 (2006).

Rockswold, S.B., G. L. Rockswold, and A. Defillo. “Hyperbaric Oxygen in Traumatic Brain Injury.” *Neurological Research*, vol. 29 (2007).

Kumaria, A., and C.M. Tolias. “Normobaric Hyperoxia Therapy for Traumatic Brain Injury and Stroke: a Review*.” British Journal of Neurosurgery*, vol. 23, no. 6 (2009).

Huang, L., and A. Obenaus. “Hyperbaric Oxygen Therapy for Traumatic Brain Injury.” *Medical Gas Research*, vol. 1, no. 21 (2011).

Bennett, M.H., B. Trytko, and B. Jonker. “Hyperbaric Oxygen Therapy for the Adjunctive Treatment of Traumatic Brain Injury (Review).” *Cochrane Database of Systematic Reviews*, vol. 12 (2012).

Beyon, C., K.L. Kiening, B. Orakcioglu, A.W. Unterberg, and O.W. Sakowitz. “Brain Tissue Oxygen Monitoring and Hyperoxic Treatment in Patients with Traumatic Brain Injury.” *Journal of Neurotrauma*, vol. 29 (2012).

McCrary, Col. B.F., L. Weaver, LCDR K. Marrs, Col. R. S. Miller, C. Dicks, K. Deru, N. Close, and Col. M. DeJong. “Hyperbaric Oxygen (HBO2) for Post-Concussive Syndrome/Chronic TBI Product Summary.” *Undersea & Hyperbaric Medicine: Journal of Undersea and Hyperbaric Medical Society*, vol. 40, no. 5 (2013).

Cossu, G. “Therapeutic Options to Enhance Coma Arousal after Traumatic Brain Injury: State of the Art of Current Treatments to Improve Coma Recovery.” *British Journal of Neurosurgery*, vol. 28, no. 2 (2014).

Wang, Y., D. Chen, and G. Chen. “Hyperbaric Oxygen Therapy Applied Research in Traumatic Brain Injury: From Mechanisms to Clinical Investigation.” *Medical Gas Research*, vol. 4, no. 18 (2014).

Interventional Studies or Clinical Trials (15 Articles)

Studies on Mild TBI (8 Articles)

DOD Funded Study (Air Force):

Wolf, G., D. Cifu, L. Baugh, W. Carne, and L. Profenna. “The Effect of Hyperbaric Oxygen on Symptoms after Mild Traumatic Brain Injury.” *Journal of Neurotrauma*, vol. 29 (2012).

DOD Funded Study (Navy):

Cifu, D.X., B.B. Hart, S.L. West, W. Walker, and W. Carne. “The Effect of Hyperbaric Oxygen on Persistent Postconcussion Symptoms.” *Journal of Head Trauma Rehabilitation*, vol. 29, no. 1 (2014).

Cifu, D.X., K.W. Hoke, P.A. Wetzel, J. R. Wares, G. Gitchel, and W. Carne. “Effects of Hyperbaric Oxygen on Eye Tracking Abnormalities in Males after Mild Traumatic Brain Injury.” *Journal of Rehabilitation Research and Development*, vol. 51, no. 7 (2014).

Cifu, D.X., W.C. Walker, S.L. West, B.B. Hart, L.M. Franke, A. Sima, C.W. Graham, and W. Carne. “Hyperbaric Oxygen for Blast-Related Postconcussion Syndrome: Three-Month Outcomes.” *Annals of Neurology*, vol. 75 (2014).

Walker, W.C., L.M. Franke, D.X. Cifu, and B.B. Hart. “Randomized, Sham-Controlled, Feasibility Trail of Hyperbaric Oxygen for Service Members with Postconcussion Syndrome: Cognitive and Psychomotor Outcomes 1 Week Postintervention.” *Neurorehabilitation and Neural Repair*, vol. 28, no. 5 (2014).

DOD Funded Study (Army):

Miller, R.S., L. K. Weaver, N. Bahraini, S. Churchill, R.C. Price, V. Skiba, J. Caviness, S. Mooney, B. Hetzell, J. Liu, K. Deru, R. Ricciardi, S. Fracisco, N.C. Close, G.W. Surrett, C. Bartos, M. Ryan, and L.A. Brenner. “Effects of Hyperbaric Oxygen on Symptoms and Quality of Life among Service Members with Persistent Postconcussion Symptoms: A Randomized Clinical Trial.” *JAMA Internal Medicine*, vol. 175, no. 1 (2015).

Israeli Study:

Boussi-Gross, R., H. Golan, G. Fishlev, Y. Bechor, O. Volkov, J. Bergan, M. Friedman, D. Hoofien, N. Shlamkovitch, E. Ben-Jacob, and S. Efrati. "Hyperbaric Oxygen Therapy Can Improve Post Concussion Syndrome Years after Mild Traumatic Brain Injury-Randomized Prospective Trial." *PLOS ONE*, vol. 8, no. 11 (2013).

United States Study:

Harch, P.G., S.R. Andrews, E.F. Fogarty, D. Amen, J.C. Pezzullo, J. Lucarini, C. Aubrey, D.V. Taylor, P.K. Staab, and K.W. Van Meter. "A Phase I Study of Low-Pressure Hyperbaric Oxygen Therapy for Blast-Induced Post-Concussion Syndrome and Post-Traumatic Stress Disorder." *Journal of Neurotrauma*, vol. 29 (2012).

Studies on Severe TBI (2 articles)

Rockswold, S.B., G.L. Rockswold, D.A. Zaun, X. Zhang, C.E. Cerra, T.A. Bergman, and J. Liu. "A Prospective, Randomized Clinical Trial to Compare the Effect of Hyperbaric to Normobaric Hyperoxia on Cerebral Metabolism, Intracranial Pressure, and Oxygen Toxicity in Severe Traumatic Brain Injury." *Journal of Neurosurgery*, vol. 112 (2010).

Rockswold, S.B., G.L. Rockswold, D.A. Zaun, and J. Liu. "A Prospective, Randomized Phase II Clinical Trial to Evaluate the Effect of Combined Hyperbaric and Normobaric Hyperoxia on Cerebral Metabolism, Intracranial Pressure, Oxygen Toxicity, and Clinical Outcome in Severe Traumatic Brain." *Journal of Neurosurgery*, vol. 118 (2013).

Studies on Non-Specified TBI (2 Articles)

Xia-yan, S., T. Zhong-quan, S. Da, and H. Xiao-ju. "Evaluation of Hyperbaric Oxygen Treatment of Neuropsychiatric Disorders Following Traumatic Brain Injury." *Chinese Medical Journal*, vol. 119, no. 23 (2006).

Sahni, T., M. Jain, R. Prasad, S.K. Sogani, and V.P. Singh. "Use of Hyperbaric Oxygen in Traumatic Brain Injury: Retrospective Analysis of Data of 20 Patients Treated at a Tertiary Care Centre." *British Journal of Neurosurgery*, vol. 26, no. 2 (2012).

Studies on Safety of Treating TBI with Hyperbaric Oxygen Therapy (3 articles)

Gossett, W.A., G.L. Rockswold, S.B. Rockswold, C.D. Adkinson, T.A. Bergman, and R.R. Quickel. “The Safe Treatment, Monitoring and Management of Severe Traumatic Brain Injury Patients in a Monoplace Chamber.” *Undersea & Hyperbaric Medicine*, vol. 37, no. 1 (2010).

Wolf, E.G., J. Prye, R. Michaelson, G. Brower, L. Profenna, and O. Boneta. “Hyperbaric Side Effects in a Traumatic Brain Injury Randomized Clinical Trial.” *Undersea & Hyperbaric Medicine*, vol. 39, no. 6 (2012).

Churchill, S., L.K. Weaver, K. Deru, A.A. Russo, D. Handrahan, W.W. Orrison, J.F. Foley, H.A. Elwell. “A Prospective Trial of Hyperbaric Oxygen for Chronic Sequelae after Brain Injury.” *Undersea & Hyperbaric Medicine*, vol. 40, no. 2 (2013).

Appendix II: Ongoing Interventional and Observational Studies on Hyperbaric Oxygen Therapy to Treat Traumatic Brain Injury (TBI)

We obtained information about eight ongoing clinical trials on the use of hyperbaric oxygen therapy to treat TBI. Information on these trials was obtained through ClinicalTrials.gov, an international registry and results database of publicly and privately supported clinical studies of human participants, which is maintained by the National Institutes of Health.[1]

We identified six interventional clinical trials on hyperbaric oxygen therapy (see table 4). The remaining two ongoing studies are observational (see table 5).[2] ClinicalTrials.gov information, such as the study start date—the date that enrollment of participants for a clinical study begins—is provided and updated by the sponsor or principal researcher of the clinical study. In addition to these ongoing studies, DOD officials told us that they are conducting additional analyses to follow up with participants from a recently funded study more than one year after their intervention to determine if any of the initial improvements observed in both the treatment and sham groups has been sustained over time.[3]

[1]ClinicalTrials.gov was created in response to the Food and Drug Administration Modernization Act of 1997, which required the Department of Health and Human Services, through NIH, to establish a registry of clinical trials information for both federally and privately funded trials of experimental drugs for serious or life-threatening diseases or conditions. Pub. L. No. 105-115, § 113, 111 Stat. 2296, 2310-12 (codified as amended at 42 U.S.C. § 282(i)). The Food and Drug Administration Amendments Act of 2007 expanded the scope of trials required to be registered and added a requirement for summary results to be submitted for some registered trials. Pub. L. No 110-85, § 801, 121 Stat. 823, 904-22 (codified as amended at 42 U.S.C. § 282(j)). The site, which was made available to the public in February 2000, included registration information for more than 198,000 clinical studies as of September 10, 2015.

[2]Interventional studies are studies in which participants are assigned to receive one or more interventions (or no intervention) so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes. The assignments are determined by the study protocol. Participants may receive diagnostic, therapeutic, or other types of interventions. An observational study is a clinical study in which participants identified as belonging to study groups are assessed for biomedical or health outcomes. Participants may receive diagnostic, therapeutic, or other types of interventions, but the researcher does not assign participants to specific interventions (as in an interventional study).

[3]As of September 2015, DOD officials told us that data collection was complete on this survey, and they were analyzing the results. However, officials did not have a date for completion of this analysis.

Table 4: Ongoing Interventional Studies on Hyperbaric Oxygen Therapy to Treat Traumatic Brain Injury (TBI), Enrolling Participants from Jan. 1, 2005 to July 22, 2015

Title	Hyperbaric Oxygen Therapy and SPECT Brain Imaging in Traumatic Brain Injury (https://clinicaltrials.gov/show/NCT00594503)
Sponsor (sponsor affiliation)	Paul G. Harch, M.D. (Louisiana State University Health Sciences Center in New Orleans)
Severity of TBI addressed in study	Not specified
Study start date and estimated study completion date[a]	January 2007 to December 2016
Purpose	to test the hypothesis that single-photon emission computerized tomography brain imaging tracks[b] and is consistent with clinical improvements in patients receiving hyperbaric oxygen therapy for chronic TBI
Title	Brain Injury and Mechanisms of Action of HBO2 for Persistent Post-Concussive Symptoms after Mild Traumatic Brain Injury (BIMA) Protocol (https://clinicaltrials.gov/show/NCT01611194)
Sponsor (sponsor affiliation)	U.S. Army Medical Research and Materiel Command
Severity of TBI addressed in study	Mild TBI
Study start date and estimated study completion date[a]	September 2012 to January 2017
Purpose	to investigate the mechanisms of action of hyperbaric oxygen therapy for persistent post-concussive symptoms[c] after mild TBI
Title	Phase 1-2 Study of Hyperbaric Treatment of Traumatic Brain Injury (https://clinicaltrials.gov/show/NCT01847755)
Sponsor (sponsor affiliation)	Barry Miskin, M.D. (Jupiter Medical Center, Florida)
Severity of TBI addressed in study	Not specified
Study start date and estimated study completion date[a]	April 2013 to April 2017
Purpose	to test the hypothesis that patients with TBI treated with hyperbaric oxygen will show improvement in function and an increased blood flow as evidenced by single-photon emission computerized tomography scan[b]
Title	Hyperbaric Oxygen Therapy Treatment of Chronic Mild Traumatic Brain Injury/Persistent Post-Concussion Syndrome (https://clinicaltrials.gov/show/NCT02089594)
Sponsor (sponsor affiliation)	Louisiana State University Health Sciences Center in New Orleans
Severity of TBI addressed in study	Mild TBI
Study start date and estimated study completion date[a]	May 2014 to March 2015[d]
Purpose	to determine whether an eight-week course of forty low-pressure hyperbaric oxygen treatments can significantly improve symptoms and cognitive function in subjects with the persistent-post concussion syndrome of mild TBI
Title	A Double-Blind Randomized Trial of Hyperbaric Oxygen Versus Sham in Civilian Post-Concussive Syndrome (https://clinicaltrials.gov/show/NCT01986205)
Sponsor (sponsor affiliation)	Lindell Weaver (Intermountain Health Care, Inc., Utah)
Severity of TBI addressed in study	Mild TBI

Study start date and estimated study completion date[a]	February 2015 to December 2018
Purpose	to examine whether 40 hyperbaric oxygen sessions have an effect on long-term symptoms after concussion
Title	Hyperbaric Oxygen Brain Injury Treatment (HBOIT) Trial (https://clinicaltrials.gov/show/NCT02407028)
Sponsor (sponsor affiliation)	Gaylan Rockswold (Minneapolis Research Foundation)
Severity of TBI addressed in study	Not specified
Study start date and estimated study completion date[a]	December 2015 to December 2017
Purpose	to determine the optimal hyperbaric oxygen treatment paradigm to be instituted in terms of atmospheric pressure, frequency of treatment and whether normobaric hyperoxia[e] following hyperbaric oxygen treatments enhances the treatment effect

Source: ClinicalTrials.gov, accessed by the National Institutes of Health on July 22, 2015. | GAO-16-154

[a]The ClinicalTrials.gov definition of "study start date" is the date that enrollment of participants for a clinical study begins and the definition of "estimated study completion date" is the anticipated date of final data collection for the last participant during the final visit to the study location.

[b]Single-photon emission computerized tomography scan is a type of nuclear imaging test, which uses a radioactive chemical and a special camera to create 3-D images of organ function.

[c]Postconcussive symptoms are physical, cognitive, and emotional or behavioral symptoms reported by individuals who suffer from mild TBI. The most commonly reported are headache, dizziness, decreased concentration, memory problems, irritability, fatigue, visual disturbances, sensitivity to noise, judgment problems, depression, and anxiety.

[d]The information for this trial had not been updated as of September 30, 2015 to indicate if it was completed or the completion date was extended and it is still ongoing.

[e]Normobaric hyperoxia is the use of oxygen at a higher-than-normal level without pressure, which results in greater oxygen content in the tissues and organs than normally exists at sea level.

Table 5: Ongoing Observational Studies on Hyperbaric Oxygen Therapy to Treat Traumatic Brain Injury (TBI), Enrolling Participants from Jan. 1, 2005 to July 22, 2015

Title	Development of Normative Datasets for Assessments Planned for Use in Patients with Mild Traumatic Brain Injury (NORMAL) (https://clinicaltrials.gov/show/NCT01925963)
Sponsor (sponsor affiliation)	Lindell Weaver (Intermountain Health Care, Inc., Utah)
Severity of TBI addressed in study	Mild TBI
Study start date and estimated study completion date[a]	October 2013 to February 2016
Purpose	to collect information about brain function and structure among active duty military personnel or civilians who are healthy. Researchers want to develop a database from normal volunteers that will be used in comparison with a similar database from active duty military with postconcussive syndrome[b] from a mild traumatic brain injury. Findings from this study may be used to design larger studies that will evaluate whether hyperbaric oxygen treatments actually improve postconcussive syndrome[b]
Title	Brain Angiogenesis (formation of new blood vessels) Induced by Hyperbaric Oxygen Therapy Can be Visualized by Perfusion MRI in Brain Injury Patients (https://clinicaltrials.gov/show/NCT02452619)
Sponsor (sponsor affiliation)	Assaf-Harofeh Medical Center

Severity of TBI addressed in study	Not specified
Study start date and estimated study completion date[a]	March 2015 to June 2015[c]
Purpose	to evaluate the perfusion magnetic resonance imaging (MRI) changes in addition to the cognitive tests before and after the treatment

Source: ClinicalTrials.gov, accessed by the National Institutes of Health on July 22, 2015. | GAO-16-154

[a]The ClinicalTrials.gov definition of "study start date" is the date that enrollment of participants for a clinical study begins and the definition of "estimated study completion date" is the anticipated date of final data collection for the last participant during the final visit to the study location.

[b]Postconcussion syndrome (or postconcussive syndrome) is when postconcussive symptoms are persistent in nature, it is also called persistent post-concussion symptoms. Postconcussive symptoms are physical, cognitive, and emotional/behavioral symptoms reported by individuals who suffer from mild TBI. The most commonly reported are headache, dizziness, decreased concentration, memory problems, irritability, fatigue, visual disturbances, sensitivity to noise, judgment problems, depression, and anxiety.

[c]The information for this trial had not been updated as of September 30, 2015 to indicate if it was completed or the completion date was extended and it is still ongoing.

Appendix III: Relevant Case Report Articles on Hyperbaric Oxygen Therapy

We identified and reviewed seven articles on case reports. Six of the seven articles focused on the effectiveness of hyperbaric oxygen therapy in treating traumatic brain injury (TBI) or post-traumatic stress disorder (PTSD). The remaining article focused on safety issues.

Table 6: Case Report Articles on Hyperbaric Oxygen Therapy to Treat Traumatic Brain Injury (TBI) or Post-Traumatic Stress Disorder (PTSD), Published from Jan. 1, 2005 to Apr. 6, 2015

Title (year)	*Pilot Case Study of the Therapeutic Potential of Hyperbaric Oxygen Therapy on Chronic Brain Injury* (2007)
Authors	Hardy, P., K.M. Johnston, L. DeBeaumont, D.L. Montgomery, J. M., Lecomete, J.P. Soucy, D. Bourbonnais, and M. Lassonde
Case(s)	1 participant with TBI (severity not specified)
Conclusion	The single-case study provided preliminary evidence of improvements after a series of 20 and 60 hyperbaric oxygen therapy treatments.
Title (year)	*Low Pressure Hyperbaric Oxygen Therapy and SPECT Brain Imaging in the Treatment of Blast-Induced Chronic Traumatic Brain Injury (Post-Concussion Syndrome) and Post-Traumatic Stress Disorder: A Case Report* (2009)
Authors	Harch, P.G., E.F. Fogarty, P.K. Staab, and K. Van Meter
Case(s)	1 participant with mild-moderate TBI, post-concussive syndrome, and PTSD
Conclusion	Hyperbaric oxygen therapy treatments caused a reduction in symptoms and signs of chronic mild or moderate blast-induced TBI, postconcussive syndrome, and PTSD. The study showed improvement of symptoms and signs of TBI, postconcussive syndrome, and PTSD reflected improvements in brain blood flow imaging.
Title (year)	*Case Report: Treatment of Mild Traumatic Brain Injury with Hyperbaric Oxygen* (2009)
Authors	Wright, Col. J,K., E. Zant, K. Groom, R.E. Schlegel, and K. Gilliland
Case(s)	2 participants (airmen) with mild TBI and post-concussive syndrome
Conclusion	Both airmen had substantive improvement within 10 days of hyperbaric oxygen treatment.
Title (year)	*Hyperbaric Oxygen Ameliorates Worsening Signs and Symptoms of Post-Traumatic Stress Disorder* (2010)
Authors	Eovaldi, B., and C. Zanetti
Case(s)	1 participant with PTSD
Conclusion	Hyperbaric oxygen therapy improved the signs and symptoms of agitation, confusion, and emotional distress in a 27-year-old male 7 days following a traumatic accident.
Title (year)	*Hyperbaric Oxygen Therapy in the Management of Paroxysmal Sympathetic Hyperactivity after Severe Traumatic Brain Injury: A Report of 6 Cases* (2011)
Authors	Lv, LQ., LJ. Hou, MK. Yu, XH. Ding, XQ Qi, and YC. Lu
Case(s)	6 participants with severe TBI
Conclusion	Symptoms of a syndrome that affects patients with severe TBI quickly disappeared after several hyperbaric oxygen therapy treatments. Five other patients with the same syndrome were then consecutively treated, and all showed positive responses.
Title (year)	*Hyperbaric Oxygen Therapy (1.5 ATA) in Treating Sports Related TBI/CTE: Two Case Reports* (2011)
Authors	K. Stoller
Case(s)	2 participants (football players) with TBI (severity not specified)

Conclusion	Two football players with TBI were shown to benefit from being treated with hyperbaric oxygen as documented by neurocognitive examinations and functional brain imaging.
Title (year)	*Tension Pneumocephalus as a Complication of Hyperbaric Oxygen Therapy in a Patient with Chronic Traumatic Brain Injury* (2012)
Authors	Lee, LC., FK. Lieu, YH. Chen, TH. Hung, and SF. Chen
Case(s)	1 participant with TBI (severity not specified)
Conclusion	Tension pneumocephalus[a] is a rare but potentially fatal complication of hyperbaric oxygen therapy. Before conducting hyperbaric oxygen therapy for a TBI patient, thorough evaluation of the patient is imperative to ensure that the expected benefits outweigh potential risks.

Source: GAO review of published articles. | GAO-16-154

Note: GAO has paraphrased the conclusions of these articles. For the complete, original version of these conclusions, refer to the articles. Full references for each article are included in appendix I.

[a]Tension pneumocephalus is a rare form of pneumocephalus in which air in the head creates a mass effect on the brain and may cause neurologic compromise, brain herniation, or even death, if not treated promptly.

Appendix IV: Relevant Literature Review Articles on Hyperbaric Oxygen Therapy

We identified and reviewed 10 articles based on literature reviews about the use of hyperbaric oxygen therapy in treating traumatic brain injuries. Eight of these articles noted that further research in the area was needed to determine if this treatment was effective. One article reported that hyperbaric oxygen therapy had positive effects when used to treat severe traumatic brain injury (TBI), another reported that the therapy can be delivered with relative safety for severe TBI.

Table 7: Literature Review Articles on Hyperbaric Oxygen Therapy to Treat Traumatic Brain Injury (TBI), Published from Jan. 1, 2005 to Apr. 6, 2015

Title (year)	*Current Controversies in the Management of Patients with Severe Traumatic Brain Injury* (2006)
Authors	Adamides, A.A., C.D. Winter, P.M. Lewis, D.J. Cooper, T. Kossmann, and J.V. Rosenfeld
Purpose	to examine the evidence base behind each intervention for TBI, including hyperbaric oxygen therapy
Conclusion	Large, multicenter, randomized trials in TBI are challenging, but are required before practice may change and outcomes improve.
Title (year)	*A Systematic Review of the Use of Hyperbaric Oxygen Therapy in the Treatment of Acute Traumatic Brain Injury* (2006)
Authors	Bennett, M. H., B. E. Trytko, and B. Jonker.
Purpose	to assess the randomized clinical evidence for the benefit or harm of adjunctive hyperbaric oxygen therapy in the treatment of acute TBI
Conclusion	Hyperbaric oxygen therapy reduced the risk of death, but there is no clear evidence of improved functional outcome. More research is needed in order to confirm or refute the findings of this review.
Title (year)	*Hyperbaric Oxygen in Traumatic Brain Injury* (2007)
Authors	Rockswold, S.B., G. L. Rockswold, and A. Defillo
Purpose	to examine historical and current investigations on the efficacy and mechanisms of hyperbaric oxygen treatment in TBI
Conclusion	Hyperbaric oxygen treatments at a depth of 1.5 atmospheres absolute (ATA) can be delivered to severe TBI patients with relative safety and low risk of oxygen toxicity.
Title (year)	*Normobaric Hyperoxia Therapy for Traumatic Brain Injury and Stroke: A Review* (2009)
Authors	Kumaria, A. and C.M. Tolias
Purpose	to survey studies, using hyperbaric oxygen therapy for TBI and stroke, which formed the basis for early studies on normobaric hyperoxia (increased oxygen without pressure). Clinical studies are presented on the efficacy of normobaric hyperoxia on TBI and stroke, emphasizing their safety, efficacy and practicality
Conclusion	Conclusions about hyperbaric oxygen therapy are limited and more research is needed. Normobaric hyperoxia (increased oxygen without pressure) has been proposed as a more feasible alternative.
Title (year)	*Hyperbaric Oxygen Therapy for Traumatic Brain Injury* (2011)
Authors	Huang, L., and A. Obenaus
Purpose	to review the experimental and clinical hyperbaric oxygen research relevant to TBI
Conclusion	Research of hyperbaric oxygen therapy in a variety of TBI models has shown positive effects. Due to the variability of human TBI, the efficacy of clinical hyperbaric oxygen therapy and an optimal regimen for hyperbaric oxygen therapy remains difficult to understand. However, all human studies have involved severe TBI patients and it is likely that there may be increased efficacy in mild or moderate TBI patients.

Title (year)	*Hyperbaric Oxygen Therapy for the Adjunctive Treatment of Traumatic Brain Injury* (2012)
Authors	Bennett, M.H., B. Trytko, and B. Jonker
Purpose	to assess studies on the effects of adjunctive hyperbaric oxygen therapy for TBI
Conclusion	In people with TBI, while the addition of hyperbaric oxygen therapy may reduce the risk of death and improve the final Glasgow Coma Scale rating[a] there is little evidence that the survivors have a good outcome. Given these findings, there is a case for additional research in order to define the true extent of the benefit of hyperbaric oxygen therapy.
Title (year)	*Brain Tissue Oxygen Monitoring and Hyperoxic Treatment in Patients with Traumatic Brain Injury* (2012)
Authors	Beyon, C., K.L. Kiening, B. Orakcioglu, A.W. Unterberg, and O.W. Sakowitz
Purpose	to summarize studies which have examined the impact of hyperbaric oxygen and normobaric oxygen (oxygen administered without pressure) on TBI patients
Conclusion	Although controlled clinical trials have not yet been carried out, the available study results suggest that a brain tissue oxygen-directed therapy may improve mortality and functional outcomes in these patients. The efficacy of oxygen-directed treatment in TBI patients remains to be proven, and further studies as well as controlled and prospective clinical trials are needed.
Title (year)	*Hyperbaric Oxygen (HBO_2) for Post-Concussive Syndrome/Chronic TBI Product Summary* (2013)
Authors	McCrary, Col. B.F., L. Weaver, LCDR K. Marrs, Col. R. S. Miller, C. Dicks, K. Deru, N. Close, and Col. M. DeJong
Purpose	to provide study researchers with information from published literature in support of prospective controlled clinical evaluations of hyperbaric oxygen treatment for persistent postconcussion syndrome following mild TBI by summarizing the relevant safety and efficacy information available from non-clinical and clinical experience to date
Conclusion	Published literature regarding hyperbaric oxygen for chronic sequelae (conditions) following TBI in adults is limited. More information from clinical trials is needed.
Title (year)	*Therapeutic Options to Enhance Coma Arousal after Traumatic Brain Injury: State of the Art of Current Treatments to Improve Coma Recovery* (2014)
Authors	Cossu, G.
Purpose	to examine the literature to clarify the indications for the various techniques and to guide the clinical practice towards an earlier coma arousal after a severe TBI
Conclusion	The selected articles had limitations due to the limited number of cases analyzed in each study. A need remains for well-designed, multicentered, and sufficiently rigorous trials enrolling specific subtypes of brain trauma to help clinicians in the everyday clinical practice and to offer the patient the best treatment protocol.
Title (year)	*Hyperbaric Oxygen Therapy Applied Research in Traumatic Brain Injury: From Mechanisms to Clinical Investigation* (2014)
Authors	Wang, Y., D. Chen, and G. Chen
Purpose	to assess the literature to examine the key role of hyperbaric oxygen therapy in treating TBI on the basis of animal studies, clinical research, complications from hyperbaric oxygen therapy and oxygen toxicity
Conclusion	Increasing evidence has shown that hyperbaric oxygen therapy is a key contributor in the treatment of TBI. The authors believe that hyperbaric oxygen therapy will be increasingly accepted by patients and approved by clinicians. Further research should be undertaken into mechanisms and efficacy of hyperbaric oxygen therapy, as it could offer a clinically promising therapeutic approach to TBI.

Source: GAO review of published articles. | GAO-16-154

Notes: GAO has paraphrased the conclusions of these articles. For the complete, original version of these conclusions, refer to the articles. Full references for each article are included in appendix I.

[a]The Glasgow Coma Scale was designed and is used to assess the depth and duration of the coma and impaired consciousness. This scale helps to gauge the impact of a wide variety of conditions, such as acute brain damage due to traumatic injuries, vascular injuries, or both.

Appendix V: Relevant Interventional Study or Clinical Trial Articles on Hyperbaric Oxygen Therapy

We identified and reviewed 15 articles on interventional studies or clinical trials. Of these, 12 articles were focused on the effectiveness of hyperbaric oxygen therapy in treating traumatic brain injury (TBI), including 8 articles on mild TBI (see table 8) and 4 articles on severe or non-specified TBI (see table 9). The remaining 3 articles are related to the safety of this treatment (see table 10).

Table 8: Eight Articles on Interventional Studies or Clinical Trials on Hyperbaric Oxygen Therapy to Treat Mild Traumatic Brain Injury (TBI) or Post-Traumatic Stress Disorder (PTSD), Published from Jan. 1, 2005 to Apr. 6, 2015

DOD-Funded Study (Air Force)	
Title (year)	*The Effect of Hyperbaric Oxygen on Symptoms after Mild Traumatic Brain Injury* (2012)
Authors	Wolf, G., D. Cifu, L. Baugh, W. Carne, and L. Profenna
Purpose	to examine the effects of 2.4 atmospheres absolute (ATA) hyperbaric oxygen on post-concussion symptoms in 50 military service members
Conclusion	This study demonstrated no improvement in symptom relief with hyperbaric oxygen at an exposure pressure of 2.4 ATA in comparison to the sham control group.[a]
DOD-Funded Study (Navy)	
Title (year)	*The Effect of Hyperbaric Oxygen on Persistent Postconcussion Symptoms* (2014)
Authors	Cifu, D.X., B.B. Hart, S.L. West, W. Walker, and W. Carne
Purpose	to examine the effects of hyperbaric oxygen on persistent postconcussion symptoms[b] in 60 military service members with at least one combat-related mild TBI
Conclusion	This study demonstrated that hyperbaric oxygen had no effect on postconcussion symptomsb after mild TBI when compared with patients in the sham control group.[a]
Title (year)	*Effects of Hyperbaric Oxygen on Eye Tracking Abnormalities in Males after Mild Traumatic Brain Injury* (2014)
Authors	Cifu, D.X., K.W. Hoke, P.A. Wetzel, J. R. Wares, G. Gitchel, and W. Carne
Purpose	to examine the effects of hyperbaric oxygen on eye movement abnormalities in 60 military servicemembers with at least one mild TBI from combat were examined
Conclusion	This study demonstrated that hyperbaric oxygen did not have an effect on eye movement abnormalities after mild TBI when compared with the sham control group.[a]
Title (year)	*Hyperbaric Oxygen for Blast-Related Postconcussion Syndrome: Three-Month Outcomes* (2014)
Authors	Cifu, D.X., W.C. Walker, S.L. West, B.B. Hart, L.M. Franke, A. Sima, C.W. Graham, and W. Carne
Purpose	to determine the effects of hyperbaric oxygen therapy after 3 months on 60 military servicemembers; whether specific subgroups may have benefited; and if no overall effect was found, whether benefit is masked by other conditions
Conclusion	This study results showed no evidence of efficacy by 3 months post-compression (after therapy) to treat the symptomatic, cognitive, or behavioral sequelae of postconcussion syndrome[c] after combat-related mild TBI.
Title (year)	*Randomized, Sham-Controlled, Feasibility Trial of Hyperbaric Oxygen for Service Members with Postconcussion Syndrome: Cognitive and Psychomotor Outcomes 1 Week Postintervention* (2014)
Authors	Walker, W.C., L.M. Franke, D.X. Cifu, and B.B. Hart

Purpose	to examine for possible effects on balance, fine motor, and cognitive performance one week after a hyperbaric oxygen intervention in 60 service members with post-concussion symptoms[b] after mild TBI
Conclusion	This study demonstrated no beneficial effect of exposure to hyperbaric oxygen therapy compared to the sham control group[a] when examining deficits associated with mild TBI and postconcussionsyndrome.[c]
DOD Funded-Study (Army)	
Title (year)	*Effects of Hyperbaric Oxygen on Symptoms and Quality of Life Among Service Members with Persistent Postconcussion Symptoms A Randomized Clinical Trial* (2015)
Authors	Miller, R.S., L. K. Weaver, N. Bahraini, S. Churchill, R.C. Price, V. Skiba, J. Caviness, S. Mooney, B. Hetzell, J. Liu, K. Deru, R. Ricciardi, S. Fracisco, N.C. Close, G.W. Surrett, C. Bartos, M. Ryan, and L.A. Brenner
Purpose	to compare the safety of and to estimate the efficacy for symptomatic outcomes from standard post concussive syndrome[c] care alone, care supplemented with hyperbaric oxygen or a sham procedure
Conclusion	This study demonstrated that hyperbaric oxygen showed no benefits over a sham control group,[a] but symptoms in both groups improved compared to servicemembers with mild TBI that did not use hyperbaric oxygen therapy.
Israeli Study	
Title (year)	*Hyperbaric Oxygen Therapy Can Improve Post Concussion Syndrome Years after Mild Traumatic Brain Injury-Randomized Prospective Trial* (2013)
Authors	Boussi-Gross, R., H. Golan, G. Fishlev, Y. Bechor, O. Volkov, J. Bergan, M. Friedman, D. Hoofien, N. Shlamkovitch, E. Ben-Jacob, and S. Efrati
Purpose	to test the effectiveness of hyperbaric oxygen therapy in improving brain function and quality of life in 50 mild TBI patients
Conclusion	This study demonstrated that hyperbaric oxygen therapy results in brain function improvements for mild TBI patients, years after injury.
United States Study	
Title (year)	*A Phase I Study of Low-Pressure Hyperbaric Oxygen Therapy for Blast-Induced Post-Concussion Syndrome and Post-Traumatic Stress Disorder* (2012)
Authors	Harch, P.G., S.R. Andrews, E.F. Fogarty, D. Amen, J.C. Pezzullo, J. Lucarini, C. Aubrey, D.V. Taylor, P.K. Staab, and K.W. Van Meter
Purpose	to report on the safety and efficacy of hyperbaric oxygen therapy in 16 military subjects with mild to moderate TBI/post-concussion symptoms[b] and PTSD
Conclusion	This study demonstrated that hyperbaric oxygen therapy was safe and that servicemembers experienced significant improvements in areas, such as physical exams and self-reporting on quality of life measurements.

Source: GAO review of published articles. | GAO-16-154

Notes: GAO has paraphrased the conclusions of these articles. For the complete, original version of these conclusions, refer to the articles. Full references for each article are included in appendix I.

[a]A sham control group is a group of participants that receives a treatment or procedure that is similar to the treatment or procedure under investigation, but is lacking the component(s) of the intervention being studied.

[b]Postconcussion symptoms are physical, cognitive, and emotional/behavioral symptoms reported by individuals who suffer from mild TBI. The most commonly reported are headache, dizziness, decreased concentration, memory problems, irritability, fatigue, visual disturbances, sensitivity to noise, judgment problems, depression, and anxiety.

[c]Postconcussion syndrome (or postconcussive syndrome) is when postconcussive symptoms are persistent in nature, such symptoms are also referred to as persistent postconcussion symptoms.

Table 9: Four Articles on Interventional Studies or Clinical Trials on Hyperbaric Oxygen Therapy to Treat Severe Traumatic Brain Injury (TBI) or Non-Specified TBI, Published from Jan. 1, 2005 to Apr. 6, 2015

Severe TBI	
Title (year)	*A Prospective, Randomized Clinical Trial to Compare the Effect of Hyperbaric to Normobaric Hyperoxia on Cerebral Metabolism, Intracranial Pressure, and Oxygen Toxicity in Severe Traumatic Brain Injury* (2010)
Authors	Rockswold, S.B., G.L. Rockswold, D.A. Zaun, X. Zhang, C.E. Cerra, T.A. Bergman, and J. Liu
Purpose	to compare hyperbaric oxygen and normobaric hyperoxia[a] treatment effects for 69 patients
Conclusion	This study demonstrated that hyperbaric oxygen has a more robust post-treatment effect than normobaric hyperoxia[a] on issues related to the brain. However, it appears that oxygen treatment for severe TBI improved over time.
Title (year)	*A Prospective, Randomized Phase II Clinical Trial to Evaluate the Effect of Combined Hyperbaric and Normobaric Hyperoxia on Cerebral Metabolism, Intercranial Pressure, Oxygen Toxicity, and Clinical Outcome in Severe Traumatic Brain Injury* (2013)
Authors	Rockswold, S.B., G.L. Rockswold, D.A. Zaun, and J. Liu
Purpose	to evaluate the combination of hyperbaric oxygen and normobaric hyperoxia[a] as a single treatment for 42 patients
Conclusion	This study demonstrated that combined hyperbaric oxygen and normorbaric hyperoxiaa treatments (increased oxygen without pressure) significantly improved brain related issues. There was also significant reduction in mortality.
Non-Specified TBI	
Title (year)	*Evaluation of Hyperbaric Oxygen Treatment of Neuropsychiatric Disorders Following Traumatic Brain Injury* (2006)
Authors	Xia-yan, S. T. Zhong-quan, S. Da, and H. Xiao-ju
Purpose	to study the effects of hyperbaric oxygen on cerebral blood flow and the usefulness of a specific type of brain images in the diagnosis and assessment of neuropsychiatric disorders[a] after TBI for 310 patients
Conclusion	This study demonstrated that a specific type of picture (image) of the brain was much more sensitive than other types in the diagnosis of neuropsychiatric disorders[b] following hyperbaric oxygen treatment of neuropsychiatric disordersb arising from TBI.
Title (year)	*Use of Hyperbaric Oxygen in Traumatic Brain Injury: Retrospective Analysis of Data of 20 Patients Treated at a Tertiary Care Centre* (2012)
Authors	Sahni, T., M. Jain, R. Prasad, S.K. Sogani, and V. P. Singh
Purpose	to determine whether addition of hyperbaric oxygen therapy to standard treatment plan of 20 patients with TBI improves outcomes
Conclusion	This study demonstrated significant improvement for patients; however, it is a retrospective study and the small numbers precludes a statistical conclusion.

Source: GAO review of published articles. | GAO-16-154

Notes: GAO has paraphrased the conclusions of these articles. For the complete, original version of these conclusions, refer to the articles. Full references for each article are included in appendix I.

[a]Normobaric hyperoxia is the use of oxygen at a higher-than-normal oxygen level without pressure, which results in greater oxygen content of the tissues and organs than normally exists at sea level.

[b]Neuropsychiatric disorders are mental disorders attributable to diseases of the nervous system.

Table 10: Three Articles on Interventional Studies or Clinical Trials on the Safety of Hyperbaric Oxygen Therapy to Treat Traumatic Brain Injury (TBI), Published from Jan. 1, 2005 to Apr. 6, 2015

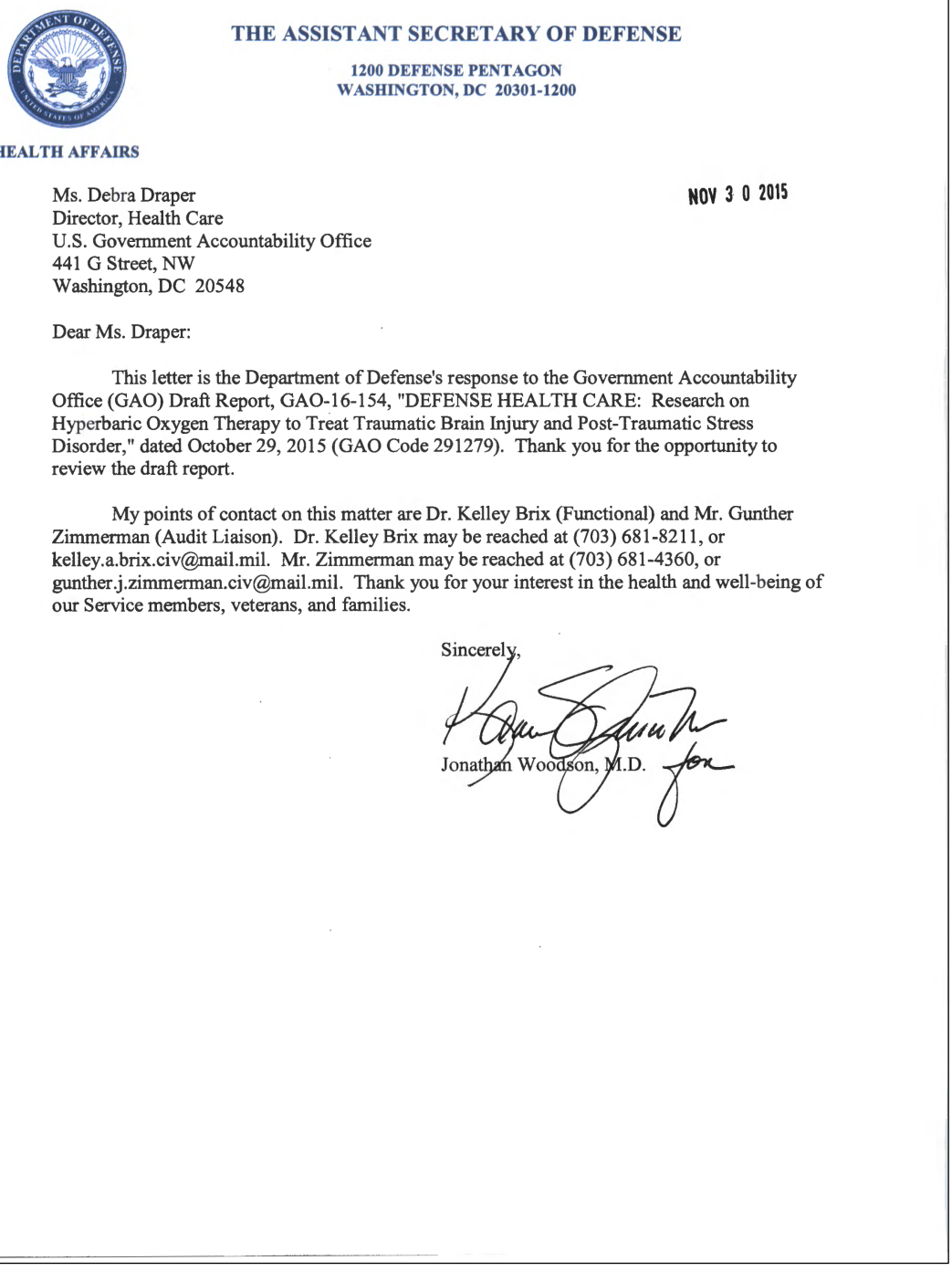
Title (year)	*The Safe Treatment, Monitoring and Management of Severe Traumatic Brain Injury patients in a Monoplace Chamber* (2010)
Authors	Gossett, W.A., G.L. Rockswold, S.B. Rockswold, C.D. Adkinson, T.A. Bergman, and R.R. Quickel
Purpose	to examine our unique experience in the management, monitoring and safety of patients with severe TBI undergoing hyperbaric oxygen treatment
Conclusion	Hyperbaric oxygen treatments at a depth of 1.5 ATA (atmospheres absolute) can be delivered repetitively to the severe TBI patient with or without multiple injuries in either a monoplace (single person) or multiplace (multi-person) chamber with relative safety.
Title (year)	*Hyperbaric Side Effects in a Traumatic Brain Injury Randomized Clinical Trial* (2012)
Authors	Wolf, E.G, J. Prye, R. Michaelson, G. Brower, L. Profenna, and O. Boneta
Purpose	to examine the side effects of 2.4 ATA hyperbaric oxygen compared to a sham control group[a] on postconcussion symptoms in military service members with combat-related, mild TBI
Conclusion	This study demonstrated no major adverse events. Given the infrequent, mild side effect profile, the authors felt the study demonstrated that hyperbaric oxygen therapy was safe at a relatively high treatment pressure in TBI subjects, and that these data could be used to evaluate the risk/ benefit calculation when deciding to utilize hyperbaric oxygen therapy for treatment of various diseases in the TBI population.
Title (year)	*A Prospective Trial of Hyperbaric Oxygen for Chronic Sequelae after Brain Injury* (2013)
Authors	Churchill, S., L.K. Weaver, K. Deru, A.A. Russo, D. Handrahan, W.W. Orrison, J.F. Foley, H.A. Elwell
Purpose	to examine recruitment, tolerance, and safety in preparation for a randomized control trial
Conclusion	The results of this study found that a brain-injured population with disability can complete a 60-session course of daily hyperbaric oxygen at 1.5 ATA for 60 minutes and can tolerate extensive testing to assess efficacy.

Source: GAO review of published articles. | GAO-16-154

Notes: GAO has paraphrased the conclusions of these articles. For the complete, original version of these conclusions, refer to the articles. Full references for each article are included in appendix I.

[a]A sham control group is a group of participants that receives a treatment or procedure that is similar to the treatment or procedure under investigation, but is lacking the component(s) of the intervention being studied.

Appendix VI: Comments from the Department of Defense



THE ASSISTANT SECRETARY OF DEFENSE

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WASHINGTON, DC 20301-1200

HEALTH AFFAIRS

NOV 3 0 2015

Ms. Debra Draper
Director, Health Care
U.S. Government Accountability Office
441 G Street, NW
Washington, DC 20548

Dear Ms. Draper:

This letter is the Department of Defense's response to the Government Accountability Office (GAO) Draft Report, GAO-16-154, "DEFENSE HEALTH CARE: Research on Hyperbaric Oxygen Therapy to Treat Traumatic Brain Injury and Post-Traumatic Stress Disorder," dated October 29, 2015 (GAO Code 291279). Thank you for the opportunity to review the draft report.

My points of contact on this matter are Dr. Kelley Brix (Functional) and Mr. Gunther Zimmerman (Audit Liaison). Dr. Kelley Brix may be reached at (703) 681-8211, or kelley.a.brix.civ@mail.mil. Mr. Zimmerman may be reached at (703) 681-4360, or gunther.j.zimmerman.civ@mail.mil. Thank you for your interest in the health and well-being of our Service members, veterans, and families.

Sincerely,

Jonathan Woodson, M.D.

Appendix VII: Comments from the Department of Veterans Affairs

DEPARTMENT OF VETERANS AFFAIRS
WASHINGTON DC 20420
November 30, 2015

Ms. Debra A. Draper
Director, Health Care
U.S. Government Accountability Office
441 G Street, NW
Washington, DC 20548

Dear Ms. Draper:

The Department of Veterans Affairs (VA) has reviewed the Government Accountability Office's (GAO) draft report, ***"DEFENSE HEALTH CARE: Research on Hyperbaric Oxygen Therapy to Treat Traumatic Brain Injury and Post-Traumatic Stress Disorder"*** (GAO-16-154). VA agrees with GAO's conclusions.

The enclosure provides general and technical comments to the draft report. VA appreciates the opportunity to comment on your draft report.

Sincerely,

Robert L. Nabors II
Chief of Staff

Enclosure

Enclosure

Department of Veterans Affairs (VA) Response to
Government Accountability Office (GAO) Draft Report
"DEFENSE HEALTH CARE: Research on Hyperbaric Oxygen Therapy to Treat Traumatic Brain Injury and Post-Traumatic Stress Disorder"
(GAO-16-154)

General Comments:

Although posttraumatic stress disorder (PTSD) is in the title of the report, there is no separate section about the literature on Hyperbaric Oxygen Therapy (HBOT) and PTSD. Though the report does acknowledge that most of the literature is about Traumatic Brain Injury and PTSD, to accurately reflect the focus of the report, the Veterans Health Administration (VHA) recommends that the abstract/executive summary includes at least one sentence about negative/inconclusive findings regarding HBOT and PTSD, and that there should be at least a small section in the body of the report about HBOT and PTSD. For example, in the abstract/executive summary, the following sentence could be added: "Based on the few published studies regarding HBOT, there is no evidence of efficacy for this treatment in well-controlled clinical trials." For a section on HBOT and PTSD, there may only need to be one or a few sentences, but it should clearly state the lack of evidence regarding HBOT as an effective treatment for PTSD.

Appendix VIII: GAO Contact and Staff Acknowledgments

GAO contact

Debra A. Draper, Director, (202) 512-7114 or draperd@gao.gov.

Staff Acknowledgments

In addition to the contact name above, Bonnie Anderson, Assistant Director; Jennie Apter; Danielle Bernstein; Leia Dickerson; Natalie Herzog; Sylvia Diaz Jones; and Emily Wilson made key contributions to this report.

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